

(43) International Publication Date
10 February 2005 (10.02.2005)

PCT

(10) International Publication Number
WO 2005/012304 A2(51) International Patent Classification⁷: C07D 487/00(21) International Application Number:
PCT/EP2004/051457

(22) International Filing Date: 12 July 2004 (12.07.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PCT/EP03/50314 16 July 2003 (16.07.2003) EP(71) Applicant (for all designated States except US):
JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): FREYNE, Eddy, Jean, Edgard [BE/BE]; c/o Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). LOVE, Christopher, John [GB/BE]; c/o Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). COOYMANS, Ludwig, Paul [BE/BE]; c/o Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). VANDER-MAESEN, Nele [BE/BE]; c/o Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). BUIJN-STER, Peter, Jacobus, Johannes, Antonius [NL/BE]; c/o Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). WILLEMS, Marc [BE/BE]; c/o Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). EMBRECHTS, Werner, Constant, Johan [BE/BE]; c/o Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE).

(74) Common Representative: JANSSEN PHARMACEUTICA N.V.; Turnhoutseweg 30, B-2340 Beerse (BE).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

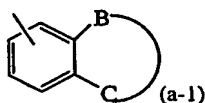
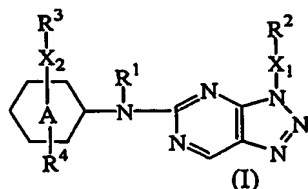
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,

[Continued on next page]

(54) Title: TRIAZOLOPYRIMIDINE DERIVATIVES AS GLYCOGEN SYNTHASE KINASE 3 INHIBITORS



(57) Abstract: This invention concerns compounds of formula (I) a N-oxide, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemically isomeric form thereof, wherein ring A represents phenyl, pyridyl, pyrimidinyl, pyridazinyl or pyrazinyl; R¹ represents hydrogen; aryl; formyl; C₁₋₆ alkylcarbonyl; C₁₋₆ alkyl; C₁₋₆ alkyloxycarbonyl; C₁₋₆ alkyl substituted with formyl, C₁₋₆ alkylcarbonyl, C₁₋₆ alkyloxycarbonyl, C₁₋₆ alkylcarbonyloxy; or optionally substituted C₁₋₆ alkyloxyC₁₋₆ alkylcarbonyl; X₁ represents a direct bond; -(CH₂)_{n3}- or -(CH₂)_{n4}-X_{1a}-X_{1b}-; R² represents optionally substituted C₃₋₇-CYC_{lo}alkyl; phenyl; a 4, 5, 6- or 7-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N; benzoxazolyl or a radical of formula (a-1); X₂ represents a direct bond; -NR¹-NR¹-(CH₂)_{n3}-; -O-; -O-(CH₂)_{n3}-; -C(=O)-; -C(=O)-(CH₂)_{n3}-; -C(=O)-NR⁵-(CH₂)_{n3}-; -C(=S)-; -S-; -S(=O)_{n1}-; -(CH₂)_{n3}-; -(CH₂)_{n4}-X_{1a}-X_{1b}-; -X_{1a}-X_{1b}-(CH₂)_{n4}-; -S(=O)_{n1}-NR⁵-(CH₂)_{n3}-NR⁵- or -S(=O)_{n1}-NR⁵-(CH₂)_{n3}-; R³ represents an optionally substituted 5- or 6-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N, or a 9- or 10-membered bicyclic heterocycle containing

at least one heteroatom selected from O, S or N; R⁴ represents hydrogen; halo; hydroxy; optionally substituted C₁₋₄alkyl; optionally substituted C₂₋₄alkenyl or C₂₋₄alkynyl; polyhaloC₁₋₃alkyl; optionally substituted C₁₋₄alkyloxy; polyhaloC₁₋₃alkyloxy; C₁₋₄alkylthio; polyhaloC₁₋₃alkylthio; C₁₋₄alkyloxycarbonyl; C₁₋₄alkylcarbonyloxy; C₁₋₄alkylcarbonyl; polyhaloC₁₋₄alkylcarbonyl; nitro; cyano; carbonyl; NR⁹R¹⁰; C(=O)NR⁹R¹⁰; -NR⁵-C(=O)-NR⁹R¹⁰; -NR⁵-C(=O)-R⁵; -S(=O)_{n1}-R¹¹-NR⁵-S(=O)_{n1}-R¹¹-S-CN; -NR⁵-CN; their use, pharmaceutical compositions comprising them and processes for their preparation.

- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*
- *of inventorship (Rule 4.17(iv)) for US only*

- *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.